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ORIGINAL RESEARCH

Clinical relevance of reports on early access programs for checkpoint inhibitors in cancer patients: a French retrospective nationwide cohort study

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Background: To accelerate access to new drugs, France operated an early access program known as Temporary Authorizations for Use (ATUs) until 2021. We analyzed clinical reports submitted under ATUs for immune checkpoint inhibitors (ICIs) and assessed their clinical relevance regarding the approval of ICIs in oncology.

Methods: We included all ICIs granted an ATU by the French drug safety agency, Agence nationale de sécurité du médicament et des produits de santé (ANSM; French National Agency for the Safety of Medicines and Health Products), for patients with cancer between 1 January 2010 and 31 December 2020. We collected patients' clinical and pharmacovigilance data from ATU reports submitted by pharmaceutical companies and compared these data with those from corresponding pivotal clinical trials (CTs).

Results: The ATUs provided early access to 5807 patients with seven ICIs across 11 cancer indications, 1 of which had no corresponding ATU report. Of the 10 available ATU reports, only 1 included all required data. Clinical follow-up forms were available for 40.5% of patients. Differences in data reporting prevented us from comparing serious adverse events between the CTs and ATU reports. Clinicians and pharmaceutical companies often disagreed on whether ICIs caused 163 permanent treatment discontinuations, with Cohen's bias- and prevalence-adjusted $\kappa = 0.52$, 95% CI 0.33-0.68. Although agreement was almost perfect for 93 nonprogressive tumor deaths ($\kappa = 0.88$, 95% CI 0.66-0.97), 29% of ATU patient deaths remained unexplained and were reported as unrelated to treatment by the pharmaceutical companies.

Conclusion: French ATUs facilitated early access to new ICIs for many patients with cancer. However, data attrition hindered effective real-world monitoring.

Key words: French early access program, real-world data, pharmacovigilance data, immune checkpoint inhibitors

INTRODUCTION

From 1994 to 2021, French patients could avail themselves of an early access program for new drugs while awaiting marketing authorization (MA), and for the setting of prices and reimbursement rates. This program was known as 'Autorisation Temporaire d'Utilisation' (Temporary Authorization for Use; ATU) until 2021, when it was renamed Early Access Authorization.

The ATUs were governed by specific rules.¹ They were requested by pharmaceutical companies and granted by the

Agence nationale de sécurité du médicament et des produits de santé (ANSM; French National Agency for the Safety of Medicines and Health Products), France's drug safety agency, for a renewable 1-year period if no other treatment was available and if treatment could not be delayed.¹ ATUs have been widely used in oncology, with half of them for cancer indications in 2016.^{2,3} During an ATU, the pharmaceutical company was required to submit regular pharmacovigilance reports.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. Today, ICIs are available in Europe for almost all solid cancers.⁴ Yet pivotal clinical trials (CTs) may overlook issues relevant to real-world patients, such as toxicity.^{5,6} Moreover, their strict inclusion criteria can result in poor external validity, and data transparency remains sub-optimal.^{7,8} As a result, some issues only emerge later, such as the rare and potentially fatal ICI-related adverse event (AE) of immune-mediated cardiomyopathy.⁹ Thus the pharmacovigilance reports that pharmaceutical companies are required

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to submit a valuable source of early real-world safety data for determining new drug prices and reimbursement rates.¹⁰

We assessed the quality and clinical relevance of the information in ATU reports versus published CTs for French patients with cancer treated with ICIs between 2010 and 2020.

METHODS

Our retrospective nationwide cohort study included all patients with cancer treated with an ICI under an ATU between 1 January 2010 and 31 December 2020. We obtained these ATU reports from the ANSM.

As previously mentioned, pharmaceutical companies were required to collect patients' follow-up forms from clinicians and submit reports to the ANSM. These reports adhered to a 'PUT' (protocole d'utilisation thérapeutique) therapeutic use protocol for safety monitoring and data collection related to ATU reports. To comply with the PUT protocol, an ATU report had to include patient and drug administration data, as well as any resulting AEs, and be circulated to clinicians, pharmacists, and regional pharmacovigilance centers.¹⁰

ATU reports were divided into two parts. The first part included a summary of clinical, demographic, and pharmacovigilance data, including the number of clinical follow-up forms received. The second part contained appendices with detailed tables for each case of toxicity (serious/nonserious and related/unrelated to the ATU drug), as well as case histories for all ICI-related serious AEs (SAEs). The ANSM defines SAEs as events that are 'fatal or life-threatening, that result in persistent or significant disability or incapacity, or that result in or prolong hospitalization'.¹¹

Treatment-related AEs were classed as either expected or unexpected based on the Summary of Product Characteristics (SmPC). The number of AE-related permanent discontinuations was reported in the summary section, and SAE-related discontinuations were detailed in the appendices.

For each ATU report, we collected the following data: the number of reports, the length of each report (in pages), and the number of tables and appendices; the number of patients who (i) applied for an ATU, (ii) were included in the program, (iii) were treated with an ICI, and (iv) had at least one clinical follow-up form filled with the ANSM; patient age, gender, and performance status (PS); the number of patients with SAEs; and the number of treatment-related deaths. For comparison, we aligned each AE item with versions 2, 3, 4, and 5 of the Common Terminology Criteria for Adverse Events (CTCAE). We considered CTCAE grades 3, 4, or 5 as SAEs when comparing ATU reports against CT data.

We also collected the number of AE-related discontinuations and all-cause deaths (except deaths from disease progression) from both the summary section and detailed appendices of the ATU reports. We analyzed the case history of each SAE that led to permanent discontinuation or death. We compared how clinicians and pharmaceutical companies assessed the link between the AE or death and treatment, measuring agreement using Cohen's kappa

statistic, adjusted for prevalence and bias according to the method described by Byrt et al.¹² (R package epiR version 2.0.68; R Foundation, Vienna, Austria).

For each indication that received an ATU, we identified the corresponding phase II or phase III CT in PubMed and compared patient characteristics and AE data between the CT article and ATU report.

All data collection was carried out by two independent reviewers, and discrepancies were resolved by a third party.

RESULTS

Clinical indications and ATU reports

Between 1 January 2010 and 31 December 2020, the ANSM granted ATUs for seven ICIs in 11 cancer indications. The median duration of the ATUs was 7 months (interquartile range 5.3-10 months). The median delay between the start of the ATUs and MA approval was 141 days (interquartile range 94-324 days; [Supplementary Table S1](https://doi.org/10.1016/j.esmooop.2024.103711), available at <https://doi.org/10.1016/j.esmooop.2024.103711>).

One ATU report was missing and excluded from our analysis. The summary sections of the remaining reports contained all the data required by the PUT protocol. One ATU report included all necessary appendices, while the appendices for the other nine reports were incomplete. As many as 9 of the 10 reports contained complete case histories for treatment-related SAEs and tables describing treatment- and nontreatment-related AEs and SAEs.

Patients included in ATU programs and CTs

Overall, 5807 patients out of 6659 applicants were accepted into an ATU program, of whom 3730 were reported as having been treated with an ICI. Pharmacovigilance reporting was incomplete. The number of patients accepted into the ATUs was available for all 10 reports analyzed, while the number of patients who received an ICI was reported in 7 of the 10 reports. The number of clinical follow-up forms received was available for 9 of the 10 reports. At least one clinical follow-up form was available for 40.5% of the included patients ([Figure 1](#)).

As many as 5 of the 10 ATU reports provided clinical data about the 5807 patients included in the ATU, but we could not determine who actually received treatment ([Table 1](#)). The other 5 reports provided data on the 3730 patients who received an ICI, as did the CT publications. In 2 of the 10 reports, we were unable to compare the ages of patients between the ATU and the CT due to the use of different metrics (mean versus median).

The CTs and ATU reports involved different patient populations. For example, for cemiplimab, the median patient age was 81 years in the ATU versus 71 years in the CT. In the case of ipilimumab for melanoma, 12.2% of patients had a PS of ≥ 2 in the ATU, while only 0.7% did in the CT. Similarly, for atezolizumab in triple-negative breast cancer and cemiplimab in cutaneous squamous-cell carcinoma, 4.6% and 6.4% of patients had a PS of ≥ 2 in the ATU, compared with 0.2% and 0% in the CT ([Table 1](#)).

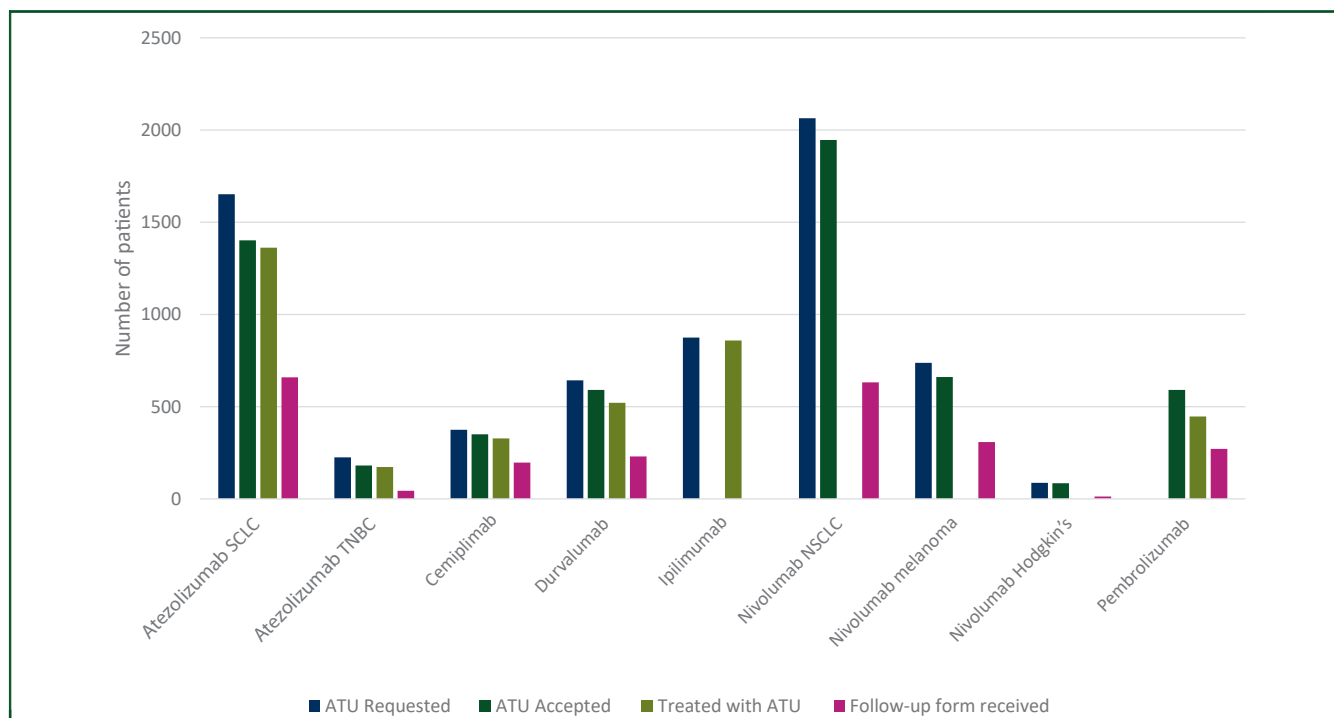


Figure 1. Number of patients for whom an ICI ATU was requested, the number for whom it was accepted, the number of patients who received the ICI drug, and the number of patients for whom a clinical follow-up form was reported to ANSM.

ANSM, Agence nationale de sécurité du médicament et des produits de santé (French National Agency for the Safety of Medicines and health products); ATU, Autorisation Temporaire d'Utilisation (Temporary Authorization for Use); ICI, immune checkpoint inhibitor; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer.

SAEs in ATU reports versus CTs

The SmPC, detailing expected and unexpected SAEs, was provided in 9 of the 10 ATU reports (Supplementary Tables S2 and S3, available at <https://doi.org/10.1016/j.esmooop.2024.103711>).

In the CT publications, SAEs were divided into treatment- or immune-related SAEs, whereas this distinction was not made in

the ATU reports. This limitation prevented us from comparing the incidence of SAEs (Supplementary Table S2, available at <https://doi.org/10.1016/j.esmooop.2024.103711>).

In the ATU reports, a mean of 14.6% (min max 0%; 32.7%) of SAEs were reported using terminology that did not match CTCAE versions 2, 3, 4, or 5, such as 'platelet disorder', 'neutrophil count abnormal', or 'throat tightness'.

Characteristics		Patients included (ATU) or randomized (CT), n	Patients provided with the ICI, n	Male, n (%)	Age, years, median (range)	Age, years, mean (range)	PS \geq 2, n (%)
Atezolizumab SCLC	CT	201	198	129 (64.2)	64 (28-90)	NA	0 (0)
	ATU	1402	1362	878 (64.5)	66 (NA-NA)	NA (25-89)	0 (0)
Atezolizumab TNBC	CT	451	452	3 (0.7)	55 (20-82)	NA	1 (0.2)
	ATU	181	173	1 (0.6)	55 (NA-NA)	NA (21-94)	8 (4.6)
Cemiplimab	CT	59	59	54 (91.5)	71 (38-93)	NA	0 (0)
	ATU	350	328	246 (75)	81 (NA-NA)	NA (17-99)	21 (6.4)
Durvalumab	CT	476	473	334 (70.2)	64 (31-84)	NA	0 (0)
	ATU	591	561	402 (68)	NA	62.4 (36-85)	NA
Ipilimumab	CT	137	131	81 (59.1)	NA	56.8 (NA-NA)	1 (0.7)
	ATU	NA	859	498 (58)	NA	59.3 (17-100)	105 (12.2)
Nivolumab squamous NSCLC	CT	135	131	111 (82.2)	62 (39-85)	NA	NA
	ATU	726	NA	583 (80.3)	66 (NA-NA)	NA (34-87)	14 (1.9)
Nivolumab non squamous NSCLC	CT	292	287	151 (51.7)	61 (37-84)	NA	0 (0)
	ATU	1220	NA	774 (63.4)	62 (NA-NA)	NA (21-100)	14 (1.1)
Nivolumab melanoma	CT	210	206	121 (57.6)	64 (18-86)	NA	1 (0.5)
	ATU	661	NA	400 (60.5)	66 (NA-NA)	NA (21-92)	13 (2)
Nivolumab Hodgkin's Lymphoma	CT	243	243	141 (58)	34 (26-46)	NA	0 (0)
	ATU	85	NA	50 (58.8)	38 (NA-NA)	NA (13-77)	NA
Pembrolizumab	CT	180	178	104 (58.4)	62 (15-87)	NA	0 (0)
	ATU	591	447	246 (55)	NA	61 (19-94)	0 (0)

ATU, Autorisation Temporaire d'Utilisation (Temporary Authorization for Use); CT, clinical trial; ICI, immune checkpoint inhibitor; NA, not applicable; NSCLC, non-small-cell lung cancer; PS, performance status; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer.

In the CTs, the mean was 1.7% (min max 0%; 6.8%) (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmooop.2024.103711>).

Treatment discontinuations

Regarding ICI discontinuations, we observed that one pharmaceutical company combined two indications into a single report (nivolumab for squamous and nonsquamous non-small-cell lung cancer). Consequently, we analyzed treatment discontinuations across nine reports, covering 10 indications.

In seven of the nine reports (78%), the rate of permanent discontinuation due to any-grade toxicity reported in the summary sections was lower than the SAE-related discontinuation rate found in the appendices (Table 2). In one of the nine reports (11%), the rate of permanent discontinuation due to AE was only available in the appendix. Notably, AE-related discontinuation rates varied significantly between the CTs and ATU reports (Table 2).

In one report, missing data prevented us from comparing how clinicians and the pharmaceutical company assessed the link between ICI treatment and SAE-related permanent discontinuations. Overall, 10 cases (6.1%) of SAE-related discontinuations were not evaluated by either the clinician or the pharmaceutical company. Among the 101 cases of SAEs that were assessed by both, opinions differed in 24 cases (23.7%). The bias- and prevalence-adjusted κ was 0.52 (95% CI 0.33; 0.68), indicating low-to-moderate agreement. In 23 (95.8%) of the 24 cases of disagreement, the pharmaceutical company classified them as treatment unrelated, whereas the clinician considered them treatment related. Of the 34 (20.9%) cases of SAE-related permanent discontinuations not analyzed by the clinician, 27 (79.4%) were reported as ICI related by the pharmaceutical company. By contrast, in the 11% of cases where clinicians did assess the link between discontinuation and treatment, they consistently concluded there was a causal relationship (Table 3 and Supplementary Table S4, available at <https://doi.org/10.1016/j.esmooop.2024.103711>).

Patient deaths not related to progressive disease

In the seven ATU reports that disclosed deaths unrelated to progressive disease (PD; i.e. non-PD deaths), we identified 93 non-PD deaths (Table 4). The link between death and treatment was evaluated in all but two cases, both from the same ATU report. Among the 49 cases assessed by both clinicians and pharmaceutical companies, there was near-perfect agreement, with a bias- and prevalence-adjusted κ of 0.88 (95% CI 0.66; 0.97; Table 4 and Supplementary Table S5, available at <https://doi.org/10.1016/j.esmooop.2024.103711>).

In four reports, covering 30 cases, the link between death and treatment was not assessed by the clinician. In 27 (90%) of those 30 cases, the pharmaceutical company classified the death as unrelated to treatment.

In four reports, some deaths had no reported cause, and no patient information was available. These 27 unexplained deaths accounted for 33.7% of all non-PD deaths in those four reports and 29% of all deaths across the seven reports. The pharmaceutical company classified these unexplained deaths as unrelated to treatment, except for two cases that were not assessed. In two reports, all deaths were attributed to PD.

DISCUSSION

In this first study of patients in the French ATU early access program for ICIs, we reviewed 10 ATU reports involving 5807 patients with cancer and seven ICIs between 2010 and 2020.

The ATU reports were hampered by substantial missing data on patient follow-up, with clinical follow-up forms absent for 59.5% of patients. Differences in AE reporting prevented us from comparing SAEs between the CTs and ATU reports, as a mean of 15% of SAEs in the ATUs did not match any CTCAE item. Inconsistencies were also noted within the ATU reports; for example, treatment discontinuation data differed between the summary and appendix. There was low to moderate agreement between clinicians and pharmaceutical companies regarding the link between

Table 2. Definitive discontinuations of ICI as reported in the initial summary section of the ATU report, appendices (narrative), and in the related phase II or III CT

ICI drug name	ATU forms, n	Definitive discontinuations for AE reported in the summary section, n (%)	Definitive discontinuations for SAE reported in appendices and narrative forms, n (%)	Discontinuation in CT, n (%)
Atezolizumab SCLC	659	15 (2.2)	6 (0.9)	22 (11.1)
Atezolizumab TNBC	44	NA	3 (6.8)	29 (6.4)
Cemiplimab	197	3 (1.5)	53 (26.9) ^a	4 (6.8)
Durvalumab	230	29 (12.6)	36 (16.7)	73 (15.4)
Ipilimumab	NA	33 (NA)	61 (NA)	17 (12.4)
Nivolumab NSCLC ^b	632	2 (0.3)	28 (4.4)	22 (10) ^c
Nivolumab melanoma	308	3 (0.9)	16 (5.1)	14 (6.8)
Nivolumab Hodgkin's	13	2 (15.4)	4 (30.8)	17 (7.0)
Pembrolizumab	271	7 (2.5)	9 (3.3)	5 (3.0)

AE, adverse event; ATU, Autorisation Temporaire d'Utilisation (Temporary Authorization for Use); CT, clinical trial; ICI, immune checkpoint inhibitor; NA, not applicable; NSCLC, non-small-cell lung cancer; SAE, serious adverse event; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer.

^aFor cemiplimab, the number of definitive SAE-related discontinuations was only provided in the text, without a table to report the characteristics of these SAEs.

^bSquamous and nonsquamous.

^cn = 5 (4%) for squamous/n = 17 (6%) for nonsquamous.

Table 3. Number of ICI discontinuations due to SAE and their treatment-relatedness as reported by the pharmaceutical company and/or by the clinician

	Total discontinuation for SAE, <i>n</i>	SAE not evaluated, <i>n</i> (%)	SAE evaluated by pharma only, <i>n</i> (%)	SAE evaluated by clinician only, <i>n</i> (%)	SAE evaluated by both pharma and clinician, <i>n</i> (%)	SAE evaluated by both and identified as treatment related by the clinician, <i>n</i> (%)	SAE evaluated by both and identified as treatment related by pharma, <i>n</i> (%)
Atezolizumab SCLC	6	3 (50.0)	1 (16.7)	0 (0)	2 (33.3)	2 (100.0)	1 (50.0)
Atezolizumab TNBC	3	1 (33.3)	0 (0)	2 (66.7)	0 (0)	NA	NA
Cemiplimab ^a	NA	NA	NA	NA	NA	NA	NA
Durvalumab	36	5 (13.9)	6 (16.7)	11 (30.6)	14 (38.9)	14 (100.0)	2 (14.3)
Ipilimumab	61	0 (0)	15 (24.6)	0 (0)	46 (75.4)	44 (95.7)	40 (87.0)
Nivolumab NSCLC	28	0 (0)	7 (25.0)	0 (0)	21 (75)	16 (76.2)	14 (66.7)
Nivolumab melanoma	16	0 (0)	2 (12.5)	0 (0)	14 (87.5)	12 (85.7)	11 (78.6)
Nivolumab Hodgkin's	4	1 (25.0)	2 (50.0)	1 (25.0)	0 (0)	NA	NA
Pembrolizumab	9	0 (0)	1 (11.1)	4 (44.4)	4 (44.4)	4 (100.0)	2 (50.0)
Total	163	10 (6.1)	34 (20.9)	18 (11)	101 (61.9)	92 (92.9)	70 (57.7)

ICI, immune checkpoint inhibitors; NA, not applicable; NSCLC, non-small-cell lung cancer; SAE, serious adverse event; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer.

^aFor cemiplimab, no information was available on the characteristics of SAEs, except the total number of SAEs (*n* = 53).

SAE-related discontinuations and ICI treatment, with 23% reported as treatment related by clinicians but not by the pharmaceutical companies. Agreement was better regarding the association between non-PD deaths and treatment. However, no information was available for 29% of non-PD deaths, all of which were reported as unrelated to treatment by the pharmaceutical companies.

ATUs had more lenient inclusion criteria than CTs, making ATU reports valuable data sources for assessing the risk-to-benefit ratio of innovative treatments.¹³ In our study, the ATU program did not detect any new safety signals, despite having at least twice as many patients receiving at least one ICI than the CTs. For example, one case of myocarditis was described in a 2019 ATU report regarding atezolizumab for small-cell lung cancer, but this was reported only after the toxicity had been reported in case reports.⁹

Under the ATU system, pharmaceutical companies were required to submit ATU reports and oversee the completion and collection of clinical follow-up forms. Clinicians were expected to complete clinical forms prospectively, providing a comprehensive assessment of graded AEs and systematically evaluating their relationship with the ICI. The prospective data collection by physicians, mimicking the case report forms of CTs, along with the centralized analysis of ATU reports, should constitute a reliable source of real-world evidence. The substantial number of missing forms may have been due to low completion rates by clinicians, attributable to the unpaid and time-consuming nature of the task, as well as a lack of incentive from drug companies. Conversely, retrospective chart reviews might suffer from missing data of interest in patient records and from the nonmedical background of those collecting the data.

Table 4. Relationship of patient death to treatment, as evaluated by the pharmaceutical company and/or clinician

	Patient deaths, <i>n</i>	Treatment-related death not evaluated, <i>n</i> (%)	Treatment-related death evaluated by pharma only, <i>n</i> (%)	Treatment-related death evaluated by clinician only, <i>n</i> (%)	Treatment-related death evaluated by both pharma and clinician, <i>n</i> (%)	Treatment-related death evaluated by both pharma and clinician and identified as treatment related by clinician, <i>n</i> (%)	Treatment-related death evaluated by both pharma and clinician and identified as treatment related by pharma, <i>n</i> (%)
Atezolizumab SCLC	4	0 (0)	2 (50.0)	1 (25.0)	1 (25.0)	1 (100)	1 (100)
Atezolizumab TNBC	0	NA	NA	NA	NA	NA	NA
Cemiplimab	6	0 (0)	0 (0)	6 (100)	0 (0)	NA	NA
Durvalumab	7	2 (28.6)	0 (0)	3 (42.9)	2 (28.6)	0 (0)	0 (0)
Ipilimumab	29	0 (0)	12 (41.4)	0 (0)	17 (58.6)	5 (29.4)	4 (23.4)
Nivolumab NSCLC	33	0 (0)	14 (42.4)	0 (0)	19 (57.6)	2 (10.5)	2 (10.5)
Nivolumab melanoma	11	0 (0)	2 (18.2)	0 (0)	9 (81.8)	1 (11.1)	1 (11.1)
Nivolumab Hodgkin's	0	NA	NA	NA	NA	NA	NA
Pembrolizumab	3	0 (0)	0 (0)	2 (66.7)	1 (33.3)	0 (0)	0 (0)
Total	93	2 (2.1)	30 (32.3)	12 (12.9)	49 (52.7)	9 (18.4)	8 (16.3)

NA, not applicable; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer.

There is growing interest in using real-world data to supplement CT results for regulatory decision making.^{14,15} However, our real-world data revealed major inconsistencies within the ATU reports, the most notable being the underestimation of AE-related discontinuations in the summaries compared with SAE-related discontinuations in the appendices (in seven of nine reports). Our study highlights the need to improve the quality of real-world data reporting to ensure the reliability of the data.

Agreement between clinicians and pharmaceutical companies regarding the link between AEs and ICI treatment was low to moderate. Under the ATU program, this link was first assessed by the clinician based on clinical and laboratory findings, and then by the pharmaceutical company based on clinical follow-up records. This discrepancy between clinicians and pharmaceutical companies highlights the limitations of AE etiology analysis in therapeutic studies. The lack of blinding in the analysis can lead to clinician attribution bias, whereas pharmaceutical laboratories may be subject to complacency bias. These biases underscore the importance of blinding in pivotal trials and the necessity of analysis by independent committees.

Conversely, there was excellent agreement between clinicians and pharmaceutical companies regarding the link between non-PD deaths and ICI treatment, despite the ATU reports lacking data on many non-PD deaths.

The CTCAE is a standardized method for classifying AEs in cancer CTs and analyzing the risk-to-benefit ratio of therapies.¹⁶ However, while the CTCAE criteria are not always applied correctly in CTs, they were also improperly utilized in the ATU reports.¹⁷

The strengths of our study lie in the prospective nature of the data and the double-blind data collection. Its main weakness is the significant amount of missing data in the ATU reports. Another limitation of the comparison between CT and ATU data is that trials include international populations, whereas ATU programs are dedicated to the French population. By law, scientific research reporting regarding patient ethnicity is not permitted in France.

Early access to therapies is crucial for the survival of oncology patients.¹⁸ For example, the French ATU programs provided early access to ATU treatments, including ICIs, for >6000 patients with advanced melanoma between 2009 and 2019.¹⁹ Over the past decade, more than half of newly approved oncology drugs were first available under an ATU.²² The French ATU system facilitated faster access to cancer therapies than the Food and Drug Administration (FDA) approval process, significantly reducing the time French patients had to wait for new treatments. Without an ATU, they would have to wait a median of 13.3 months for MA approval and an additional mean of 485 days for drug pricing.²⁰⁻²² Although FDA approval of new cancer therapies does not always guarantee clinical benefit, the ATU programs seem to have provided most French patients with cancer with such benefits.²³⁻²⁵

Rapid access must be weighed against the cost of innovative therapies. Under the ATU system, pharmaceutical companies were free to set drug prices, even when MA

approval was uncertain. This may have reduced the pressure on pharmaceutical companies to obtain MA. In addition, it may have skewed subsequent drug prices.²⁶

The French early access system was overhauled in 2021 to streamline procedures, accelerate access, and strengthen data collection.²⁷ Patients are now required to complete self-reported quality of life questionnaires to mitigate the underestimation of their symptoms and quality of life by clinicians.²⁸ Computerized forms have also helped clinicians improve data collection. In addition, pharmaceutical companies must now offer financial incentives based on data completeness, with the aim of reducing missing clinical follow-up forms to <10%. French health authorities may suspend an ATU if data collection in the reports is inadequate.

Conclusion

ICIs have revolutionized cancer treatment. The French ATU programs provided patients with early access to these innovative drugs, enabling >3500 patients across 11 cancer indications to be treated between 2010 and 2020. However, the ATU programs were hampered by inconsistent and variable reporting of real-world clinical data, which undermined the clinical relevance of the ATU reports. The recent reform of the early access program in France aims to improve this reporting process.

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DISCLOSURE

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DATA SHARING

Requests to access data should be made to the French National Agency for Medicines and Health Products Safety.

REFERENCES

1. Article L5121-12 — Code de la santé publique — Légifrance. Available at https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000041721215/2020-10-01. Accessed September 6, 2023.
2. Rapport d'information : médicaments innovants: consolider le modèle français d'accès précoce. . Available at <https://www.senat.fr/rap/r17-569/r17-5691.pdf>. Accessed February 20, 2024.
3. de Launet Q, Brouard A, Doreau C. Les autorisations temporaires d'utilisation (ATU) : 50 ans d'histoire de l'évolution de la réglementation des médicaments en France. *Rev Hist Pharm*. 2004;92(341):47-54.
4. Tableau Software. Chronology of EU approvals of anti-PD-1/L1 antibodies. Available at https://public.tableau.com/views/GlobalPD-1L1approval_timeline_15722872918340/PD-1approvalandscape?%3Adisplay_static_image=y&%3AbootstrapWhenNotified=true&%3Aembed=true&%3Alanguage=fr-FR&:embed=y&:showVizHome=n&:apiID=host0#navType=0&navSrc=Parse. Accessed February 14, 2024.

5. Lopes GS, Tournigand C, Olswold CL, et al. Adverse event load, onset, and maximum grade: a novel method of reporting adverse events in cancer clinical trials. *Clin Trials Lond Engl*. 2021;18(1):51-60.
6. Kempf E, Bogaerts J, Lacombe D, Liu L. 'Mind the gap' between the development of therapeutic innovations and the clinical practice in oncology: a proposal of the European Organisation for Research and Treatment of Cancer (EORTC) to optimise cancer clinical research. *Eur J Cancer*. 2017;86:143-149.
7. Osipenko L, Ul-Hasan SA, Winberg D, et al. Assessment of quality of data submitted for NICE technology appraisals over two decades. *BMJ Open*. 2024;14(2):e074341.
8. Hopkins AM, Modi ND, Abuhelwa AY, et al. Heterogeneity and utility of pharmaceutical company sharing of individual-participant data packages. *JAMA Oncol*. 2023;9(12):1621-1626.
9. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749-1755.
10. Article R5121-70 — Code de la santé publique — Légifrance. Available at https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000045166651/2021-01-01. Accessed February 14, 2024.
11. ANSM. Glossaire ANSM. . Available at <https://ansm.sante.fr/glossaire/E>. Accessed March 18, 2024.
12. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol*. 1993;46(5):423-429.
13. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;16(1):495.
14. Cave A, Kurz X, Arlett P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. *Clin Pharmacol Ther*. 2019;106(1):36-39.
15. Skovlund E, Leufkens HGM, Smyth JF. The use of real-world data in cancer drug development. *Eur J Cancer*. 2018;101:69-76.
16. United States Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE) v5.0*. Washington, DC: United States Department of Health and Human Services; 2017.
17. Zhang S, Liang F, Tannock I. Use and misuse of Common Terminology Criteria for Adverse Events in cancer clinical trials. *BMC Cancer*. 2016;16(1):392.
18. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol*. 2019;20(11):1493-1505.
19. Christen C, Belgodère L, Guillot B, et al. Access to innovation through the national early access program and clinical trials for patients with malignant melanoma. *Cancer*. 2021;127(13):2262-2270.
20. Hartmann M, Mayer-Nicolai C, Pfaff O. Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. *Crit Rev Oncol Hematol*. 2013;87(2):112-121.
21. Newton M, Scott K, Troein P. *EFPIA Patients W.A.I.T. Indicator 2021 Survey*. Brussels: EFPIA.
22. Jacquet E, Kerouani-Lafaye G, Grude F, et al. Comparative study on anticancer drug access times between FDA, EMA and the French Temporary Authorisation for Use program over 13 years. *Eur J Cancer*. 2021;149:82-90.
23. Pham FY-V, Jacquet E, Taleb A, et al. Survival, cost and added therapeutic benefit of drugs granted early access through the French Temporary Authorization for Use program in solid tumors from 2009 to 2019. *Int J Cancer*. 2022;151(8):1345-1354.
24. Vivot A, Jacot J, Zeitoun JD, Ravaud P, Crequit P, Porcher R. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000-2015. *Ann Oncol*. 2017;28(5):1111-1116.
25. Brinkhuis F, Goettsch WG, Mantel-Teeuwisse AK, Bloem LT. Added benefit and revenues of oncology drugs approved by the European Medicines Agency between 1995 and 2020: retrospective cohort study. *BMJ*. 2024;384:e077391.
26. Degrossat-Théas A, Paubel P, Parent De Curzon O, Le Pen C, Sinègre M. Temporary Authorization for Use: does the French patient access programme for unlicensed medicines impact market access after formal licensing? *Pharmacoeconomics*. 2013;31(4):335-433.
27. Décret n° 2021-869 du 30 juin 2021 relatif aux autorisations d'accès précoce et compassionnel de certains médicaments. Available at <https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000043728288>. Accessed June 30, 2021.
28. Di Maio M, Gallo C, Leigh NB, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. *J Clin Oncol*. 2015;33(8):910-915.